Prostate Cancer Therapeutics and Their Complications: A Primer for the Primary Care Provider

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INTRODUCTION

Prostate cancer is the most common malignancy in men and the second leading cause of cancer mortality in men. Even with evolving alterations in the screening guidelines, the annual number of prostate cancers per year in the United States remains substantial. The majority of men diagnosed with prostate cancer will die of other causes. Many men will face survivorship issues related to prior therapies. In addition, advanced prostate cancer has a long natural history with continuous exposure to therapies that have impactful effects on overall health. The primary care provider is an integral participant in the care team for the prostate cancer patient. The goal of the ensuing discussion is to provide an educational primer on prostate cancer therapeutics and potential consequences of therapy.

RADIATION THERAPY

Radiation techniques have evolved, resulting in a reduced rate of acute and late toxicities.[1] Radiation therapy primarily is delivered by two methods: external beam radiation treatment (EBRT) and brachytherapy. Most men treated with EBRT for localized prostate cancer, either primary treatment or salvage treatment after surgery, have an excellent prognosis with cancer specific survival longer than 10 years. Therefore, monitoring for acute and late toxicities from treatment is paramount. We herein discuss the pattern and timing of toxicities associated with radiation treatment for prostate cancer. Of note: many men receiving EBRT for treatment of prostate cancer also receive androgen deprivation therapy (ADT). The effects of ADT will be discussed in a separate section.

Typical acute toxicities of EBRT include fatigue, urinary symptoms and gastrointestinal symptoms. Acute cutaneous toxicity, as often seen in radiation for breast cancer, is exceedingly rare in prostate cancer as the skin is spared significant radiation. Fatigue is the most common symptom of radiation therapy, occurring in 40–80% of patients treated. Fatigue often arises within the first several weeks of radiation therapy and may last several months beyond the completion of radiation therapy. Severity of fatigue varies but the majority of patients are able to maintain a full work schedule. Incontinence is less likely to occur with radiation therapy than prostatectomy; however, dysuria, urinary frequency and nocturia are more common. Symptoms can mimic urinary tract infection and urinalysis may often reveal microscopic hematuria and even the presence of WBCs. Antibiotic therapy is indicated only in the uncommon circumstance in which bacteria is noted and cultured. Typical acute GI toxicities during radiation therapy include intermittent loose stools or diarrhea. Common management strategies include use of anti-diarrheal agents and dietary/nutritional changes. Data supporting the benefit of nutritional changes is overall weak but strategies that have shown efficacy include fat restriction, lactose restriction, fiber supplementation, or a combination of the above.[2] Acute toxicity predicts late gastrointestinal events.[1,3]

The Prostate Testing for Cancer and Treatment (ProtecT) trial assessed toxicity outcomes in 1600 men randomized to active surveillance, radical prostatectomy, or EBRT with short term ADT. The toxicity analysis distinguished the toxicities of prostatectomy and EBRT as compared to the non-treatment patients. Patients receiving EBRT reported no increase in urinary incontinence as opposed to all patients immediately postoperative. Although higher rates of voiding symptoms and nocturia were noticed at 6 months post-radiation treatment, at one year the rates were similar to active surveillance patients. Reports on erectile quality after EBRT revealed decreased erection quality at 6 months with a continued erection quality decline over the 6-year follow-up period. Overall long-term erectile dysfunction rates in radiation patients were similar to what was experienced by active surveillance patients. Patients with erectile dysfunction after treatment should be referred to a multidisciplinary clinic where patients receive care from medical, surgical and psychology providers. A multidisciplinary Men's Health Clinic is available for patients at the Lifespan Cancer Institute. Increased rates of rectal bleeding were shown after radiation therapy after 2 years of follow-up. There was no increase in fecal incontinence.[4]

There are significant differences between brachytherapy and external beam radiation therapy. Only selected patients are considered appropriate for brachytherapy as primary treatment. Since minimal radiation is delivered beyond the prostate capsule, brachytherapy is offered only for the best prognostic categories. Placement of the brachytherapy seeds is done in an operating room with patients under general anesthesia. Patients must be in good health in order to undergo this invasive procedure. Anticoagulation and

anti-platelet therapy need to be discontinued for the procedure. Toxicities also differ between the two radiation methods. When compared to active surveillance patients, there was a clinically significant increase in urinary obstruction and irritation scores at 3 and 12 months for brachytherapy but only at 3 months for external beam radiation therapy. At 24 months, all patients had similar rates. Patients with significant pre-existing urinary symptoms or large prostate glands (greater than 40cc–60cc) have increased rates of irritative urinary symptoms after brachytherapy and are more appropriate patients for EBRT. There was no relative effect on urinary continence seen in either radiation arm. Clinically significant increased bowel problems were seen in the external beam population at 3 months. No increased bowel problems were seen with brachytherapy. While in many studies erectile function is better for patients receiving brachytherapy as opposed to EBRT, other studies do not show a substantial difference.[5,6] Finally, there are safety guidelines that are given to patients after brachytherapy that restrict prolonged, close contact (such as sitting on the lap) with young children and pets for patients receiving brachytherapy, as the seed implants emit radiation for several months after placement. During this time, brachytherapy patients will set off alarms on security detectors and patients should forewarn security officials by showing proper documentation.

Later toxicities (greater than 6 months from treatment) occur in approximately 10% of patients who had received EBRT. The most common late gastrointestinal effect is proctitis. This typically presents with rectal bleeding and less commonly rectal urgency or tenesmus. First-line treatments include oral agents such as pentoxyfylline, vitamin A, metronidazole, 5-ASA as well as topical agents such as sucralfate, hydrocortisone, and formalin. Endoscopic approaches include argon plasma coagulation or heater probe or laser. Hyperbaric oxygen treatments may also be helpful in refractory cases.[7,8] Currently, hydrogel rectal spacers are used to reduce the radiation dose exposure to the rectum. Current data is mixed on clinical effectiveness of rectal spacers while it certainly increases the cost of treatment and exposes the patient to an additional invasive procedure. The most common late genitourinary effect is radiation cystitis. It usually presents as self-limited gross hematuria that can be persistent and severe. Treatment options include conjugated estrogens, pentosan polysulfate, or topical formalin. Referral to urologic consultants is recommended for endoscopic cautery or laser ablation and to exclude other causes of hematuria. Rarely, bleeding leads to the need for transfusion support and hospitalization for bladder irrigation. If severe bleeding persists, the patient may require a surgical diversion and/or cystectomy. Hyperbaric oxygen treatments may also be helpful in refractory cases, usually referred by radiation oncologists.[9,10]

Therapeutic ionizing radiation has the risk of radiation-induced secondary malignancies. In prostate radiation, the most common secondary malignancies are bladder cancer, colorectal cancer, and pelvic sarcomas. Secondary hematologic malignancies, such as acute leukemias and myelodysplastic syndromes, are relatively uncommon. Malignancies typically develop 5 to 20 years following treatment. Smoking enhances the risk of bladder cancer. Retrospective historical data noted a 6% increase in relative risk of secondary solid tumor after radiation relative to surgery. The relative risk was increased to 15% for those who survived more than 5 years after treatment and to 34% for those who survived greater than 10 years. The estimated absolute risk of radiation-induced solid tumor was 1 in 290 with rates as high as 1 in 70 in men surviving more than 10 years after treatment.[11] A more recent SEER analysis by Krasnow and colleagues revealed an increased secondary malignancy risk at 10 years risk from 1.9 to 2.7% and at 20 years from 3.6 to 5.4%. This risk was most increased in patients younger than 55 years even after adjusting for competing risk factors and life expectancy.[12] The risk appears to be dependent on treatment technique and "conformity" (precise radiation field) as demonstrated in a third SEER database review by de Gonzalez and colleagues. This demonstrated a statistically significant decrease in secondary rectal cancers with 3D conformal technique compared with 2D planning. There were also decreased rates of colon cancer and leukemia with brachytherapy relative to external beam radiation.[13] There are currently no secondary malignancy screening recommendations for men that have received radiation therapy to the prostate/pelvis, but a primary care physician should be aware of this risk and work up any concerning symptoms such as hematuria or hematochezia.

ANDROGEN DEPRIVATION THERAPY

The main drivers of prostate cancer cell growth and survival are androgens. Androgen deprivation therapy (ADT) is the backbone of therapy for patients with various presentations of prostate cancer. It is the cornerstone of treatment of incurable, metastatic disease. ADT slows down progression to metastatic disease in patients with non-metastatic disease and a rising PSA after local treatment (biochemical relapse). ADT is an adjunctive treatment to radiation for certain higher-risk patients with prostate cancer being treated with curative intent. ADT is also utilized in select cases after prostatectomy as adjuvant therapy. The duration of ADT can vary from 4 months to continuous ADT depending on the clinical situation and treatment objectives. In general, the longer the duration of ADT the more troublesome the adverse effects.

Androgen deprivation therapy can be achieved by bilateral orchiectomy or luteinizing hormone release hormone (LHRH) therapy. In the United States, medical castration through LHRH antagonist or agonist injections is more commonly employed. Degarelix is a LHRH antagonist

administered as monthly subcutaneous injections. Degarelix achieves castration, defined as serum testosterone levels of less than 50 ng/dL, within 3 days. Since it has a relative rapid onset of action, it is often the choice for patients with acute complications of prostate cancer, such as urinary obstruction, severe bone pain or spinal cord compression. Degarelix requires monthly injection and has a 40% rate of local injection reactions. Leuprolide is a LHRH agonist that induces castration in 2 to 4 weeks. It has a lower rate of local injection reaction (1%) than degarelix. It may be given monthly or every 3, 4 or 6 months. Leuprolide can cause an initial testosterone surge that may accelerate the growth of prostate cancer cells in the first 2 to 4 weeks after its administration. Thus, it requires concurrent androgen receptor antagonism to prevent exacerbated bone pain, spinal cord compression and urinary obstruction from prostate tumor growth. The most common oral antagonist receptor antagonist in current use is bicalutamide. Bicalutamide has an elimination half-life of 7 days; therefore, a lead-in of 14 days is usually sufficient to address the testosterone surge.

Androgen deprivation therapy has been linked to metabolic syndrome. Testosterone suppression induces skeletal muscle mass loss. This happens in part due to downregulation of insulin growth factor receptors and regulation of transcription factors associated with skeletal muscle programmed death. Lean muscle mass loss is implicated in insulin resistance and subsequent hypercholesterolemia and hyperglycemia. Upregulation of lipoprotein lipase is also observed in the castrate state. Hypertension is thought to be a result of a higher basal level of endothelin-1, a hormonal vasoconstrictor.[14] Studies have shown that the risk of diabetes in patients on ADT is increased by 44% compared to matched control patient cohort not receiving ADT. The risk for coronary artery disease and for myocardial infarct is increased 16% and 11% respectively. Effect on cardiovascular mortality is mixed and inconclusive.[15] Degarelix may have a lower risk of cardiac events at 1 year compared with leuprolide in men with pre-existing cardiovascular disease, based on a retrospective study.[16] An ongoing prospective American study (the PRONOUNCE trial) is assessing longer-term, cardiovascular outcomes in patients on degarelix versus leuprolide. The time of a cardiovascular event from the initiation of ADT does affect risk, with a decline in risk with passage of time.[17] Physical activity has been shown to decrease the risk for cardiovascular events in men on ADT.[18]

Bone loss is a known adverse effect of ADT. This is due to dysregulation of Receptor Activator of Nuclear Factor Kappa beta (RANK) and its ligand (RANKL), both important for bone resorption.[19] RANKLs are secreted by osteoblasts and bind to RANK on osteoclasts to activate osteolysis. The RANKL monoclonal antibody denosumab blocks this interaction. Men on ADT are at higher risk for bone fractures. A baseline Dual-Energy X-ray Absorptiometry (DEXA) scan should be obtained at the onset of ADT. Thereafter, DEXA scans are recommended every 1–2 years. Men with osteoporosis at baseline or after androgen deprivation therapy should be treated with the RANKL blocker denosumab 60 mg intravenously every 6 months or the intravenous bisphosphonate zoledronic acid 4 mg yearly or the oral bisphosphonate alendronate 70 mg weekly.[20,21] Bisphosphonate treatment is contraindicated in patients with severe renal impairment and should be used with caution in patients with mild to moderate renal impairment. Men who are older than 50 years old with osteopenia and a World Health Organization FRAX score (available online) predicting a 10-year risk of hip fracture equal or above 3% or major osteoporosis-related fracture equal and above 20%, should be treated in a similar manner. A baseline 25-OH vitamin D level is recommended. Patients who are deficient in vitamin D require appropriate replacement therapy. Decrease of alcohol consumption, smoking cessation and exercise are important to counteract bone resorption and men should be counseled to adopt these beneficial, lifestyle measures.

Men with bone metastasis are at risk for pathological fractures, spinal cord compression and bone pain; collectively referred to as skeletal-related events (SREs). ADT compounds the risk of SREs by activating osteoclasts.[19] Bisphosphonates and RANKL inhibitors have shown to delay skeletal-related events but only in men with metastatic bone lesions and castrate-resistant disease (mCRPC).[22] Dosing bone protective agents for mCRPC patients is frequent; thus, increasing the risk of osteonecrosis of the jaw (ONJ) to 2%–4%. Dental preventative care is important in preventing ONJ and dental providers need to be informed that men are receiving therapy. Dental extractions increase the risk of developing ONJ and should occur only as a necessity. If a tooth extraction is required, bone protective agents should be held for an extended period. Other common side effects from these agents include myalgias and arthralgias, flu-like symptoms, hypocalcemia for denosumab and renal insufficiency for zoledronic acid.

In summary, skeletal-related events and metabolic syndrome figure among the most significant long-term adverse effects of androgen deprivation therapy. It is the role of the health care providers to recognize the magnitude of the skeletal and cardiovascular risks associated with these important prostate cancer therapies. By mitigating contributing cardiovascular factors and reinforcing fracture prevention, primary care providers have an opportunity to promote bone and cardiovascular health.

ANTI-ANDROGEN AGENTS

Over the last two decades, a significant change in the management of prostate cancer is the development of new therapeutics for mCRPC and the expansion of their roles in the treatment of metastatic castrate sensitive prostate cancer (mCSPC). The scope of this discussion will be limited

to the two most commonly utilized anti-androgen agents: abiraterone acetate and enzalutamide.

Abiraterone acetate was approved for the treatment of mCRPC in 2011 and mCSPC in 2018. In both circumstances, abiraterone improves overall survival and progression-free survival with its bigger impact in mCSPC, which has placed the drug earlier in the treatment paradigm.[24] The mechanism of action of abiraterone is unique. Abiraterone is an androgen biosynthesis inhibitor, that impedes 17 α-hydroxylase/C17,20-lyase (CYP17). CYP 17 catalyzes the formation of dehydroepiandrosterone (DHEA) and androstenedione. Treatment with LHRH agents and orchiectomy reduces testosterone production from the testis only, with abiraterone providing added blockade from the adrenal glands and prostate cancer cells. Absorption of abiraterone increases if administered with fats and it should be administered on an empty stomach. A significant consequence of treatment with abiraterone is development of mineralocorticoid excess syndrome (MES) as a result of accumulated CYP 17 substrates being shuttled to the mineralocorticoid pathway. This can lead to complications of hypertension, fluid retention and hypokalemia. Co-administration of prednisone at 5mg to 10mg per day mitigates MES but adds the toxicities of continuous steroid administration. Even with prednisone administration, hypertension remains a common adverse effect. In an analysis of 5445 patients from 5 studies, the overall incidences of all-grade hypertension and high-grade hypertension (grade 3 and 4) were 21.9% (95% CI: 13.6–33.2%) and 10.2% (95% CI: 6.9–11.6%) respectively.[25] Of note, there is no standard management of abiraterone treatment-related hypertension. Finally, abiraterone was associated with a statistically significant 76% (RR 1.76) increase in the risk of high-grade cardiac disorder adverse events (95% CI: 1.12-2.75 RR; $p = 0.01$) and in a 28% (RR 1.28) increase in all-grade cardiac disorder adverse events (95% CI: 1.06-1.55; $p = 0.01$). [26]

Enzalutamide was approved for the treatment of mCRPC in 2012, non-metastatic or M0 CRPC in 2018 and mCSPC in 2019.[27] Similar to abiraterone, enzalutamide impacts overall survival and progression-free survival in these indications; moving to an earlier point in the treatment paradigm. Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Like abiraterone, it is combined with ADT. Enzalutamide's most common adverse effect is fatigue. Enzalutamide is associated with less hypertension when compared to abiraterone and is not associated with a statistical increase in cardiac events.[26] However, there is a small risk of seizures (0.1%–1%) and is not recommended for patients with a history of seizures. Finally, falls have been associated with enzalutamide.

Drug-drug interactions can occur with either abiraterone or enzalutamide. Abiraterone inhibits liver cytochrome P450 (CYP)-dependent enzymes CYP2C8 and CYP2D6, which are involved in the metabolism of approximately 25% of all drugs. Thus, abiraterone may increase plasma levels of CYP2C8 substrates including amiodarone and carbamazepine and CYP2D6 substrates, including amitriptyline, oxycodone and risperidone. Enzalutamide induces CYP3A4, CYP2C9 and CYP2C19, which metabolize up to 50% of medications. Importantly, enzalutamide may decrease plasma levels of warfarin and clopidogrel. As always, cross-referencing medications for drug-drug interactions remains a critical component of patient care requiring cross discipline communication among providers.

CONCLUSION

The aging of our population and the high prevalence of prostate cancer will result in an increase in prostate cancer patients actively treated and prostate cancer survivors. Proper long-term surveillance of prostate cancer patients involves the monitoring of late gastrointestinal, genitourinary and sexual side effects, the surveillance for secondary malignancies associated with radiation therapy, monitoring for cardiovascular disease, diabetes and osteoporosis. In summary, awareness of the timing, frequency and severity of these effects helps the clinician to provide high quality care for the man with prostate cancer.

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